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Brain dysfunctions: Shared mechanisms in fragile X syndrome, autism and schizophrenia

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Several psychiatric conditions such as schizophrenia, autism and intellectual disabilities share the same brain cell abnormalities: the contacts (synapses) between brain cells are poorly developed and not functional. Claudia Bagni and her group associated with the VIB, KU Leuven, and Tor Vergata University in Italy, in collaboration with leading laboratories in the Netherlands, France, USA and UK have unraveled how a single protein (CYFIP1) orchestrates two biological processes to form proper contacts between brain cells. Importantly, the researchers identified various proteins that are important for the balance of the two processes and associated with several neurological disorders. Their study is published in the leading journals *Neuron*.

Claudia Bagni (VIB/KU Leuven/Tor Vergata-Rome): "These findings provide insights into the shaping of our brain and have important consequences for further studies of conditions such as autism, schizophrenia and intellectual disabilities. This work has a substantial impact considering that 1 in 5 Europeans is confronted with one of these brain conditions ranging from mild to serious developmental disabilities.

Synapses are essential for communication between brain cells

Our brain contain more than 100 billion brain cells (neurons) that contact each other in the so-called synapses, the place where signals are

passed from one cell to the other. Synapses are like small "relay stations" containing around 2000 proteins that need to be regulated in a very controlled manner. Any small dysfunction of this cellular area can result in a brain disease. Autism, schizophrenia and intellectual disabilities (Down Syndrome, Fragile X Syndrome, Alzheimer Disease) are only a few examples of brain conditions that are linked to poorly functioning synapses.

The Fragile X Syndrome

Claudia Bagni and her team have pioneered the molecular studies on the Fragile X Syndrome, the leading cause of inherited intellectual disability. Patients often show autistic-like behavior, anxiety, aggression, hyperactivity and self-injurious behavior. The condition is caused by the absence of the Fragile X Mental Retardation protein (FMRP) that is involved in supplying the correct building blocks for the synapse. Claudia Bagni's team had previously demonstrated that FMRP forms a complex with CYFIP1 to regulate this supply.

Shaping our synapses

Bagni's group has now identified a key function of CYFP1 at synapses. CYFIP1 orchestrates two biological processes: together with FMRP, it acts to regulate the protein supply at synapses and when bound to another complex (WRC), controls actin polymerization, a scaffold of brain cells. These findings lead to the "hub" model, in which the same complex, having CYFIP1 at the center, might be affected in apparently different diseases. A disrupted balance between the two functions results in abnormal contacts between brain cells. Silvia De Rubeis, Emanuela Pasciuto and Claudia Bagni (VIB/KU Leuven/Tor Vergata-Rome) have exposed the molecular mechanisms that ensure that this balance is maintained.

The important function of CYFP1 was underlined further by the discovery that many proteins that interact with CYFP1 were already associated with (hereditary forms of) brain conditions. The VIB scientists suggest that mutations in the proteins working together with CYFIP1 might perturb the balance of the interaction networks thereby triggering a spectrum of pathological processes at synapses that can lead to a broad range of clinical manifestations such as intellectual disabilities , autism and schizophrenia. This study offers new perspectives for a better understanding of these still not understood brain conditions.

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